

### **Remarks/Arguments**

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-124 are pending in this application and are rejected on various grounds. Claims 122 and 124 have been canceled without prejudice or disclaimer. Claim 119 has been amended for clarity. The rejections to the presently pending claims are respectfully traversed.

### **Priority**

Applicants rely on the gene amplification assay for patentable utility of the instant invention, which was first disclosed in U.S. Provisional Application 60/141037, filed June 23, 1999, priority to which has been claimed in this application. Hence, the present application is entitled to at least the priority date of **June 23, 1999**.

### **Information Disclosure Statement**

Applicants submit an IDS separately enlisting references recited in the Blast report in order to be compliant with 37 C.F.R. § 1.98(a)(1). Consideration of this Information Disclosure Statement is respectfully requested.

### **Specification**

A. The disclosure was objected to by the Examiner as containing “embedded hyperlink and/or other form of browser-executable code.” The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

B. Applicants have amended the title to better describe the claimed invention.

Accordingly, Applicants believe that the objections to the specification should be withdrawn.

### **Claim objections**

A. Applicants have amended claims 119 to remove references to Figures in the claim language. Hence this objection should be withdrawn.

### **Claim Rejections – 35 USC § 101 and 35 USC § 112, first paragraph**

Claims 119-124 are rejected under 35 U.S.C. §101 allegedly because "the instant application does not disclose a specific and substantial biological role of this protein or its significance." Claims 119-124 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention". Applicants respectfully disagree with and traverse these rejections.

The Examiner asserts that since the protein of the invention is not supported by a specific and substantial asserted utility or well established utility, the claimed antibodies also lack utility.

### **Utility Standard**

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial"

utility.” (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P. 2107 II (B) (1) gives the following instruction to patent examiners: “If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, the Utility Guidelines restate the Patent Office’s long established position that any asserted utility has to be “credible.” “Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant’s assertions.” (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

### Arguments

As discussed under the section on "priority", Applicants rely on the gene amplification data for patentable utility for this case, which was first disclosed in U.S. Provisional Application 60/141037, filed June 23, 1999, and hence, the effective filing date for the present application should at least be **June 23, 1999**. Applicants further assert that the PRO1281 protein and its antibodies have utility and provide basis for this assertion below.

Gene amplification is an essential mechanism for oncogene activation and the assay is well-described in Example 170, page 539 of the present application. The gene amplification data shows that genomic DNA was isolated from a variety of primary cancers and cancer cell lines listed in Table 9 (especially page 554, Table 9C) which includes primary colon cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9A. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C indicates that PRO1281 showed approximately 1.07-1.15 ΔCt units which corresponds to  $2^{1.07}$ - $2^{1.15}$ - fold amplification or **2.099 fold to 2.219-fold** amplification in colon tumors, which is significant and thus the PRO1281 gene has utility as a diagnostic marker of human lung cancer.

Applicants further submit that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack *et al.*, who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-,

mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that gene amplification correspondingly increases mRNA expression, in general.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of amplified genes, the combined teachings in the art exemplified by Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, and the Polakis declaration overwhelmingly teach that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO1281 gene, that the PRO1281 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1281 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

Claimed proteins would have diagnostic utility even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO1281, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1281 polypeptide, for example, in detecting over-expression or absence of expression of PRO1281. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides.

Accordingly, Applicants submit that antibodies to PRO1281 have utility based on the gene amplification assay. Thus, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

**Claim Rejections – 35 USC § 112, second paragraph**

A. Claims 122 was rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner alleges that it was unclear how an antibody can be both an antibody and a fragment.

Applicants have canceled claim 122 and amended claim 119 to recite "an antibody, or a fragment thereof," as suggested by the Examiner and therefore this rejection should be withdrawn.

B. Claim 124 was rejected for reciting "specifically binds" especially since, claim 119 recites "binds." Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled claim 124 and amended claim 119 to recite "specifically binds."

Applicants submit that the term "specific binding" or "specifically binds" has a well established meaning, and is understood by those skilled in the art to mean that the antibody binds to a particular polypeptide, and does not significantly bind to another polypeptide. Since claim terms should be given their ordinary, art-recognized meaning, the present rejection is believed to be misplaced, and should be withdrawn.

**Claim Rejections – 35 USC § 102**

A. Claims 119-124 are rejected under 35 U.S.C. §102(b) as being anticipated by Baker (WO99/63088- dated December 1999).

Since Applicants are entitled to at least the effective priority date of **June 23, 1999**, Baker is neither 35 U.S.C. §102(b) nor 102(a) art. Hence, Applicants respectfully request that this request be withdrawn.

B. Claims 119-124 are rejected under 35 U.S.C. §102(a) as being anticipated by Tang (WO01/53312- dated July 2001).

As discussed above, based on the effective priority date of at least **June 23, 1999**, Tang is not prior art. Thus, this rejection should be withdrawn.

**Claim Rejections – 35 USC § 103**

A. Claims 119-124 are rejected under 35 U.S.C. §103(a) as being unpatentable over Weimann (2001) in view of Baker (1999).

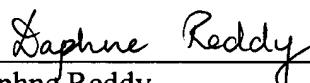
As discussed above, based on the effective priority date entitled to this application, the primary reference Baker falls as prior art and so does Weimann. Therefore, present claims are not obvious over Baker or Weimann and hence, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C26). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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